The management of B3 lesions with emphasis on lobular neoplasia

Abeer Shaaban

Queen Elizabeth Hospital Birmingham
NHSBSP core biopsy categories

- **B1** - Normal
- **B2** - Benign
- **B3** – Uncertain malignant potential
- **B4** – Suspicious of Malignancy
- **B5** – Malignant
B3 category

• Proportion: 5-9% of core biopsy diagnoses

• Includes lesions of variable significance.

• Diagnostically challenging!

• Includes lesions with and without atypia.

• Requires further sampling: traditionally by surgery.
B3 lesions

- FEA
- AIDP
- Lobular in situ neoplasia
- Papilloma
- Radial scar
- Fibroepithelial lesion
- Mucocoele like lesion
- Other: spindle cell lesions, apocrine atypia...
Factors affecting frequency & upgrade rate

- Patient population: screening vs symptomatic
- Method of biopsy: NCB vs VAB (gauge of needle)
- Type and combination of B3 lesion
- Size of lesion
- Presence/absence of atypia
<table>
<thead>
<tr>
<th>Lesion</th>
<th>Without atypia</th>
<th>With atypia</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without atypia</td>
<td>3.8% Noyak et al 2013</td>
<td>5% Youk et al 2011 (age, size)</td>
<td></td>
</tr>
<tr>
<td>With atypia</td>
<td>33% (vs 3%) McGhan et al 2013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial scar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without atypia</td>
<td>(4-9%)</td>
<td></td>
<td>Histopathology 2008;52:650, Brenner et al 2002</td>
</tr>
<tr>
<td>With atypia</td>
<td>(24-44%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucocoele-like lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without atypia</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With atypia</td>
<td>21% Rakha et al, Histopathology 2013</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### UPGRADE RATES: FEA + AIDP

<table>
<thead>
<tr>
<th>Study</th>
<th>FEA</th>
<th>FEA + AIDP</th>
<th>AIDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al (2010)</td>
<td>14%</td>
<td>29%</td>
<td>37%</td>
</tr>
<tr>
<td>Rakha et al (2011a, b)</td>
<td>21%</td>
<td>29%</td>
<td>50.4%</td>
</tr>
<tr>
<td>Rajan et al (2011)</td>
<td>14%</td>
<td>29%</td>
<td>40%</td>
</tr>
<tr>
<td>Total</td>
<td>18%</td>
<td>29%</td>
<td>44%</td>
</tr>
</tbody>
</table>
Why is there need for B3 management standardisation?
1. Management is inconsistent across screening units.

2. Increasing use of VAB

3. Over-treatment is a recognised issue

4. Local guidelines: Leeds, London QARC
National survey to all breast screening units in England

• 46 breast screening units responded (58% response rate)

• Filled out by:
  Radiologist – 40
  Clinician – 4
  Radiographer – 2

• 28 units perform First line vacuum assisted biopsy (VAB)
• 37 units performed Second line VAB
B3 lesions with no atypia – radial scar/papilloma with no atypia

• If conventional 14G core biopsy shows B3 lesion with no atypia
  – 34 units responded
  – 74% will offer second line VAB
  – 26% will offer Surgical Diagnostic Biopsy

• If 1st line VAB shows B3 lesion with no atypia
  – 27 units
  – 41% will offer second line VAB
  – 44% will offer Surgical biopsy
  – 15% will discharge due to adequate sampling
# Management of B3 lesion with atypia on 14G core biopsy

<table>
<thead>
<tr>
<th>Lesion Description</th>
<th>2nd line VAB</th>
<th>Surgical biopsy</th>
<th>Discharge</th>
<th>EC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEA</td>
<td>66</td>
<td>34</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AIDP</td>
<td>53</td>
<td>47</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AIDP + FEA</td>
<td>56</td>
<td>44</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ALH</td>
<td>57</td>
<td>34</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>LCIS</td>
<td>51</td>
<td>40</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Radial scar + atypia</td>
<td>37</td>
<td>63</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Papilloma + atypia</td>
<td>40</td>
<td>60</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
### Management of B3 lesion with atypia on VAB

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>2nd line VAB</th>
<th>Surgical biopsy</th>
<th>Discharge</th>
<th>EC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEA</td>
<td>39</td>
<td>50</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>AIDP</td>
<td>28</td>
<td>69</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>AIDP + FEA</td>
<td>28</td>
<td>69</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>ALH</td>
<td>46</td>
<td>46</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>LCIS</td>
<td>39</td>
<td>46</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Radial scar + atypia</td>
<td>24</td>
<td>76</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Papilloma + atypia</td>
<td>21</td>
<td>79</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Benign open biopsies

UK benign open biopsy rates

1.73 per 1,000 women screened (Prevalent)
0.48 per 1,000 women screened (Incident)

UK average: 1.74
Target: 1.0
Minimum std: 1.5
Leeds prevalent open biopsy rate: 0.9
Increasing use of VAB
Core samples

With thanks to Dr. Nisha Sharma
Vacuum-assisted core biopsy of breast lesions of uncertain malignant potential (B3) – an alternative to surgery in selected cases

Tennant et al. Breast 2008;17:456
Papillary lesions and radial scars without atypia
Over-treatment is a recognised issue
B3 Positive predictive value

- 21%  Dillon et al 2007 (Ireland)
- 20%  El-Sayed et al 2008
- 25%  Rakha et al 2011 1025 (NCB)
- 21.2% Bianchi et al 2011 3107 cases (VACNB Study group, Italy)
- 20%  Strachan et al 2015, under review, 398
The majority of patients (75-80%) with B3 diagnosis will have a benign histology on further sampling.

Is surgical excision necessary?
Local guidelines such as London QARC and Leeds pathway have been developed.
Local guidelines

London Region Quality Assurance Reference Centre
Guidance on management of indeterminate breast lesions

Authors:  
Dr LS Wilkinson,  SWLBSS
Dr Clive Wells,  UCL
Dr W Teh,  NLBSS
Mr A Desai,  SELBSS
Dr R Wilson,  The Royal Marsden Hospital and SWLBSS
on behalf of London Region QARC

January 2012

There are clear recommendations on the management of both benign and malignant lesions in the breast, but the management of lesions that may develop into, or be associated with an increased risk of malignancy is less easy, and the traditional surgical approach of excision may not always be the optimal management.
New patient pathway using vacuum-assisted biopsy reduces diagnostic surgery for B3 lesions

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a Department of Radiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK
b Department of Histopathology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

AIM: To assess the clinical impact of a new patient management pathway incorporating vacuum-assisted biopsy for lesions of uncertain malignant potential (B3).

MATERIALS AND METHODS: A retrospective analysis was undertaken of all B3 lesions on core biopsy in the pathology database from April 2008 to April 2010. Outcome measures assessed included final histological diagnosis, frequency of diagnostic surgical biopsy, and impact on management.

RESULTS: In the old pathway, there were 95 B3 lesions, of which 14% (13/95) were planned for vacuum-assisted biopsy and 86% (82/95) for surgical biopsy. In the new pathway, there were 94 B3 lesions, of which 68% (64/94) were planned for vacuum-assisted biopsy and 32% (30/94) for surgical biopsy. Following further sampling with vacuum-assisted biopsy, only 13% of patients required diagnostic surgical biopsy and in 25% of cases, a preoperative diagnosis of carcinoma was reached allowing patients to proceed to therapeutic surgery.

CONCLUSION: The new pathway has reduced the number of benign diagnostic surgical biopsies performed and increased the preoperative diagnosis of breast cancer.
Leeds pathway for B3 lesion with atypia
Aim to adequately sample by VAB to rule out coexistent cancer

Follow up
Lobular neoplasia

- Encompasses atypical lobular hyperplasia (ALH) and lobular in situ carcinoma (LCIS).

- LCIS: classical and variants
Classical LCIS

- Disease of premenopausal women (90%)
- Most LCIS diagnosed between 40-50 yrs.
- Often multifocal (60-80%) and bilateral (up to 35%)
- True incidence is difficult to assess
  (reported between 0.5-3.8% (Haagenson 1978, Page 1991))
Classical LCIS

- Presents on mammographic screening but can also be incidental.
- Risk of malignancy is x3 likely to be unilateral than bilateral (Page et al 2003)
LCIS

- Marker of breast cancer risk: RR 8-10
- Direct precursor:
  
  LOH: in LCIS and the associated lobular ca:

Mutation of the e-cadherin gene: in LCIS and
invasive lobular ca, Berx et al., 1996
Histologically

- A monomorphic proliferation within TDLU of dyscohesive cells with uniform round nuclei, indistinct nucleoli and scant cytoplasm.

- Intracytoplasmic lumina are often present.

- Pagetoid spread can be seen.
- **Type A cells**: small uniform cells with bland nuclei and scant cytoplasm

- **Type B cells**: cells are larger, with more cytoplasm and mild to moderate atypia
Type B
E-cadherin
ALH vs LCIS

- Depends on extent of lesion

- LCIS: more than half of the acini are filled, distended and distorted by the dyscohesive lobular cells.
DD: LCIS vs DCIS

- Cellular cohesion
- Look for architectural pattern of DCIS
- E-cadherin
E-cadherin
Variants of LCIS

Pleomorphic LCIS (PLCIS)
A more recently recognized variant of Lobular Carcinoma In Situ (LCIS)

May calcify hence present through breast screening

Biology and natural history uncertain

Histologically: mimics high grade DCIS
E-cadherin
Rare variant of LCIS

LCIS with comedo necrosis

A study of 18 cases reported a strong association with invasive ca (67% of cases)

LCIS upgrade rate

- Ranged from 0-60%, (majority 2-25%), Buckley et al 2014 systematic review, Murray et al 2013

- Upgrade rate 3% in concordant and 38% if imaging-pathological discordant, Murray et al 2013.

- ALH upgrade rate (27%) not significantly different from LCIS (33%), Ibrahim et al 2012
Reasons for variation

- Screening vs symptomatic
- Radiological correlation
- Amount of tissue: core vs VAB
- LCIS in structured lesions
- Family history vs sporadic
- Inclusion of PLCIS
- Co-existing other lesions as ADH
Upgrade rate of PLCIS

41%, range 30-60%, Hussain and Cunnick 2011, Carder et al 2011
Variability in LN management

- **Surgical excision**: as some patients may have a co-existing invasive malignancy
  
  (ABS/BASO guidelines 2009)

- **Observation/radiological monitoring**: LN without radiological pathological discordance
  
  (Meroni et al 2014)

- **Surgical excision mandatory only if radiological-pathological discordance**
  
  (Capobianco et al 2014)

- **VAB** as alternative to surgical excision
  
  (Parkin et al 2014)
B3 guidelines group

- Commissioned by NHSBSP
- Invited members representing imaging, surgery and pathology
Composition of the B3 group

- **Chair**: Prof Sarah Pinder
- **Radiologists**: Louise Wilkinson, Nisha Sharma
- **Surgeons**: Simon Pain, Anil Desai, Ashu Gandhi
- **Pathologists**: Sarah Pinder, Andrew Lee, Abeer Shaaban
B3 Guidelines Group

Remit

- To undertake review of the literature on lesions categorised as B3
- To come up with guideline document for a practical approach to management of these for the NHS BSP.
Progress

- First meeting: October 2014
- Management recommendations lesion by lesion.
- Use of diagrams/flow charts
- General principles: radiological/pathological concordance
- Draft for discussion/consultation
Recommendations

- 2nd line VAB as method of choice for further sampling of B3 lesions, following either conventional core or 1st line VAB B3 diagnosis.
- All cases should be discussed at MDT meeting
- Centres should plan to acquire 2nd line VAB or refer to a centre that can do it
- Diagnostic excision for fibroepithelial lesions, spindle cell lesions, papilloma with atypia
Advantages of 2\textsuperscript{nd} line VAB

For patients

- Targeted sampling: less tissue removed.
- Outpatient procedure, well tolerated by patients.
- Avoid complication of anaesthesia and surgery
- No scarring, easier further imaging and assessment.
- Rapid turnaround of results.
Advantages of 2nd line VAB For MDT

- Improves pre-operative diagnosis rate.
- Reduces benign surgical biopsy rate.
- Planning therapeutic surgery for cancer patients.
- Reducing the risk of over-treatment
Reduction in benign diagnostic surgery

From Dr S Rajan
Lobular neoplasia on core biopsy

- ALH/Classical LCIS: code as B3 and recommend further tissue examination by VAB
- PLCIS: code as B5a and manage as DCIS
- LCIS with necrosis: rare, best coded as B4, recommend surgical excision.
How to deal with extensive calcification?
Sample two ends/areas of the lesion by 1st line VAB

If B3, proceed to 2nd line VAB
Does the management vary in presence/absence of atypia?
49 cases of radial scar without atypia

In 9 cases (18.3%): atypia on surgical excision.

Conclusion: diagnosis of RS without atypia does not exclude malignancy. Further sampling by VAB or surgical excision is required.
<table>
<thead>
<tr>
<th>Reason for B3 diagnosis on NCB</th>
<th>No (% of the total)</th>
<th>Benign</th>
<th>Malignant in-situ</th>
<th>Malignant invasive</th>
<th>PPV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial Atypia present²</td>
<td>511 (50)</td>
<td>304</td>
<td>144</td>
<td>63</td>
<td>40.5</td>
</tr>
<tr>
<td>Pure ADH</td>
<td>248</td>
<td>121</td>
<td>92</td>
<td>33</td>
<td>50.4</td>
</tr>
<tr>
<td>Pure FEA</td>
<td>24</td>
<td>19</td>
<td>4</td>
<td>1²</td>
<td>20.8</td>
</tr>
<tr>
<td>Atypia unspecified</td>
<td>189</td>
<td>119</td>
<td>46</td>
<td>24</td>
<td>37.0</td>
</tr>
<tr>
<td>All LN</td>
<td>79</td>
<td>56</td>
<td>8</td>
<td>15</td>
<td>29.1</td>
</tr>
<tr>
<td>Pure ALH</td>
<td>33</td>
<td>25³</td>
<td>3</td>
<td>5</td>
<td>24.2</td>
</tr>
<tr>
<td>Pure LCIS</td>
<td>20</td>
<td>17³</td>
<td>1</td>
<td>2</td>
<td>15.0</td>
</tr>
<tr>
<td>LN unspecified</td>
<td>8</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>LN and ADH</td>
<td>13</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>61.5</td>
</tr>
<tr>
<td>LN and RS/CSL</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>60.0</td>
</tr>
<tr>
<td>No Epithelial Atypia (other B3 lesions)</td>
<td>514 (50%)</td>
<td>459</td>
<td>33</td>
<td>22</td>
<td>10.7</td>
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<tr>
<td>Papillary lesion</td>
<td>185 (18)</td>
<td>154</td>
<td>24</td>
<td>7</td>
<td>16.7</td>
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<tr>
<td>With atypia</td>
<td>30</td>
<td>19</td>
<td>10</td>
<td>1</td>
<td>36.7</td>
</tr>
<tr>
<td>Without atypia</td>
<td>155</td>
<td>135</td>
<td>14</td>
<td>6</td>
<td>12.9</td>
</tr>
<tr>
<td>RS/CSL</td>
<td>329 (32)</td>
<td>284</td>
<td>26</td>
<td>19</td>
<td>13.6</td>
</tr>
<tr>
<td>With atypia</td>
<td>51</td>
<td>31</td>
<td>12</td>
<td>8</td>
<td>39.2</td>
</tr>
<tr>
<td>Without atypia</td>
<td>278</td>
<td>253</td>
<td>14</td>
<td>11</td>
<td>8.9</td>
</tr>
<tr>
<td>FE lesions</td>
<td>52 (5)</td>
<td>51⁸</td>
<td>0</td>
<td>1</td>
<td>1.9</td>
</tr>
<tr>
<td>B3 miscellaneous</td>
<td>52 (5)</td>
<td>44</td>
<td>4</td>
<td>4</td>
<td>15.4</td>
</tr>
<tr>
<td>Total</td>
<td>1,025</td>
<td>763</td>
<td>177</td>
<td>85</td>
<td>25.6</td>
</tr>
</tbody>
</table>

Rakha et al 2014
Does the management vary if B3 lesion shows atypia vs no atypia?

- Overall: No
- Further sampling is required for papillomas/radial scars without atypia (unless lesion completely removed radiologically)
- Guidelines recommend excision of papilloma with atypia to assess size (for DCIS size cut off)
Does the pathway differ if first sample is by conventional core or VAB?
No

The purpose of the first biopsy (14 g core or VAB) is to obtain a small sample to make a diagnosis.
If a centre is doing first line VAB sampling, should they still do 2\textsuperscript{nd} line VAB for B3 lesions?
Yes

First line VAB is a limited sample for initial diagnosis. An adequate, representative sample to exclude malignancy cannot be achieved by 1st line VAB
Positive predictive value for malignancy on surgical excision of breast lesions of uncertain malignant potential (B3) diagnosed by stereotactic vacuum-assisted needle core biopsy (VANCB): A large multi-institutional study in Italy

- 22 Italian centres
- 3107 B3 VAB diagnoses
- 1644 (54.2%) underwent surgical excision
- Overall PPV: 21.2 %
<table>
<thead>
<tr>
<th>Lesion</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure ADH</td>
<td>27.3</td>
</tr>
<tr>
<td>FEA</td>
<td>12.7</td>
</tr>
<tr>
<td>ALH</td>
<td>24.2</td>
</tr>
<tr>
<td>LIN</td>
<td>22</td>
</tr>
<tr>
<td>RS</td>
<td>10.6</td>
</tr>
</tbody>
</table>
What if a unit cannot implement 2\textsuperscript{nd} line VAB?
Units should try to implement 2nd line VAB

Otherwise, they should refer to another centre that provides the service.

The group felt they should recommend what is best for patients.
■ Majority of UK units have 1\textsuperscript{st} line VAB

■ It is hoped that the guidelines will be a catalyst to enable units to justify a business case and implement the pathway
Should 2nd line VAB aim to excise the whole lesion?
Not necessarily, depending on size

The aim is to obtain further tissue and a representative sample to exclude co-existent malignancy

The group will provide guidance on what represents adequate sampling
Should we therefore aim to always extensively sample on 1\textsuperscript{st} line VAB/sample all calcification?
No. 1<sup>st</sup> line VAB/cores are meant to provide a small sample for diagnosis and not to remove the whole abnormality.

It may be feasible to fully sample a small area of calcification.

However, it would not be justified to excessively sample all patients by 1<sup>st</sup> line VAB.
How much tissue should be taken by second line VAB?
Standard is: 12-20 cores, 7 or 8g needle, or equivalent to 3.5 gm

2nd line VAB is targeted sampling. While tissue taken is less than a diagnostic excision, it is likely to be more representative
Should incidental lesions such as incidental ALH, LCIS, ADH...be managed using the same pathway?
Yes

Evidence show that those lesions are associated with upgrade to malignancy on further tissue sampling
Characterization and outcome of breast needle core biopsy diagnoses of lesions of uncertain malignant potential (B3) in abnormalities detected by mammographic screening

- Two UK regions: West Midlands and South Central region
- Final histology: 25% malignant
<table>
<thead>
<tr>
<th>Lesion</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure ADH</td>
<td>50.4</td>
</tr>
<tr>
<td>LCIS</td>
<td>15</td>
</tr>
<tr>
<td>ALH</td>
<td>24.2</td>
</tr>
<tr>
<td>LN (unspecified)</td>
<td>25</td>
</tr>
<tr>
<td>LN+ADH</td>
<td>61.5</td>
</tr>
<tr>
<td>LN+CSL/RS</td>
<td>60</td>
</tr>
<tr>
<td>Papilloma with atypia</td>
<td>36.7</td>
</tr>
<tr>
<td>Papilloma without atypia</td>
<td>12.9</td>
</tr>
<tr>
<td>RS with atypia</td>
<td>39.2</td>
</tr>
<tr>
<td>RS without atypia</td>
<td>8.9</td>
</tr>
</tbody>
</table>
How should small incidental papilloma and/or radial scar without atypia be managed?
If no atypia and the lesion is small and fully excised on core/VAB, categorise as B2.

If not sure is completely excised, code as B3 and discuss at MDT meeting. If confirmed wholly excised, no further action is needed.

If not wholly excised, follow the management pathway by 2nd line VAB
Summary

- Current management of B3 lesions is not uniform and likely to represent overtreatment.

- The majority of lesions are benign on excision.

- MDT discussion and radiological-pathological correlation are essential for planning management.
B3 guidelines are pending and recommend the use of 2\textsuperscript{nd} line VAB for further sampling as alternative to diagnostic surgery, except if lesion is completely removed by 1\textsuperscript{st} line VAB.
THANK YOU